Drug-free holidays: Compliance, tolerability, and acceptability of a 3-day atovaquone/proguanil schedule for pre-travel malaria chemoprophylaxis in Australian travellers

Colleen L Lau [1,2], Lani Ramsey [3], Laura Mills[2], Luis Furuya-Kanamori [1,4], Deborah J Mills[2]

[1] Research School of Population Health, The Australian National University, Canberra, Australia

[2] Dr Deb The Travel Doctor, Travel Medicine Alliance, Brisbane, Australia

[3] Travel-Bug Vaccination Clinic, Travel Medicine Alliance, Adelaide, Australia

[4] Department of Population Medicine, College of Medicine, Qatar University, Doha, Qatar

Corresponding author:

Dr Colleen Lau

Research School of Population Health

The Australian National University

62 Mills Rd, Acton 0200, ACT, Australia.

Email: colleen.lau@anu.edu.au.

Phone: +61 402134878

Summary: When used as pre-travel malaria chemoprophylaxis to enable a 'drug-free holiday', the 3-day atovaquone/proguanil schedule (250mg/100mg, 4 tablets/day for 3 consecutive days) had a high compliance rate of 97.7%, and was well tolerated and accepted by travellers.

Abstract

Background: Poor compliance with chemoprophylaxis is a major contributing factor to the risk of malaria in travellers. Pre-travel chemoprophylaxis may improve compliance by enabling 'drug-free holidays'. The standard treatment dose of atovaquone/proguanil (250mg/100mg, 4 tablets/day for 3 days) provides protection against malaria for at least 4 weeks, and could therefore potentially be used for pre-travel chemoprophylaxis. In this study, we assessed the compliance, tolerability, and acceptability of the 3-day atovaquone/proguanil schedule for malarial chemoprophylaxis.

Methods: 233 participants were recruited from four specialised travel medicine clinics in Australia. Adults travelling to malaria-endemic areas with low/medium risk for ≤4 weeks were enrolled, and prescribed the 3-day schedule of atovaquone/proguanil, completed at least one day before departure. Questionnaires were used to collect data on demographics, travel destination, medication compliance, side effects, and reasons for choosing the 3-day schedule. The study was registered with the Australian and New Zealand Clinical Trials Registry, number ACTRN12616000640404

Results: Overall, 97.7% of participants complied with the 3-day schedule. Although side effects were reported in 43.3% of the participants, these were well tolerated, and mainly occurred during the first and second day. None of the participants developed malaria. The main reasons for choosing the 3-day schedule over standard chemoprophylaxis options were that it was easier to remember (72.1%), required taking fewer tablets (54.0%), and to help scientific research (54.0%).

Conclusions: The 3-day atovaquone/proguanil schedule had an impressively high compliance rate, and was well tolerated and accepted by travellers. Further studies are required to assess the effectiveness of this schedule for chemoprophylaxis in travellers.

Keywords: malaria, chemoprophylaxis, atovaquone, proguanil, travel

Introduction

Malaria is an important cause of severe illness and preventable deaths in travellers [1,2]. An estimated 30,000 cases of travel-related malaria are reported annually [1]. In a study of ~7000 returned travellers with fever at GeoSentinel clinics, malaria was the most common diagnosis, accounting for 21% of cases and 33% of fatalities [3]. The mainstay of malaria prevention in travellers is the use of chemoprophylactic medications; a number of effective drugs are available and currently recommended schedules involve taking medications before, during, and after travel to a malaria-endemic area [4]. Atovaquone/proguanil is one of three commonly prescribed medications for chemoprophylaxis; the standard adult dosage is one tablet (250mg/100mg) per day, starting 1-2 days before arriving in a malaria-endemic area, and continuing daily until 7 days after leaving [4]. The other two commonly used medications are doxycycline (adult dose 100mg/day, starting 1-2 days before arriving in a malaria-endemic area, and continuing until 4 weeks after leaving) and mefloquine (adult dose 250mg/week, starting at least 2 weeks before arriving in a malaria-endemic area, and continuing until 4 weeks afterwards) [4].

Although effective medications are available for malaria chemoprophylaxis, their effectiveness is often compromised by poor compliance [5]. Most cases of travel-related malaria are associated with poor compliance or complete failure to take chemoprophylaxis. Studies around the world have found poor compliance amongst the full spectrum of travellers including tourists [6], backpackers [7], expatriate workers [8,9], military personnel [10-12], volunteers [13] and those returning to home countries to visit friends and relatives (VFR) [14]. A study of imported malaria in Australia found that of 246 cases, only 56% took chemoprophylaxis, and of these only 29% were fully compliant [15]. Failure to take chemoprophylaxis and poor

compliance have also been associated with an increased risk of severe malaria and malaria-related deaths [16-18].

Improving compliance with malaria chemoprophylaxis could therefore significantly reduce the risk of travel-related malaria and deaths. Poor compliance is at least partly due to the need to take medications for long periods of time. Multiple studies have found that forgetting to take medications was a common problem [19,20], so compliance could potentially be improved by using simpler medication schedules, such as shorter duration, less doses, or schedules that can be completed before travel [5,21]. In 2007, a group of travel medicine and malaria experts highlighted the need to explore pre-travel malaria chemoprophylaxis regimens, or 'drug-free holidays', to improve compliance [5]. However, little progress has been made in the past decade.

Atovaquone/proguanil is highly effective for treating malaria when given at a dose of 1000mg/400mg (4 tablets) per day for 3 consecutive days (referred to henceforth as the 3-day schedule). In malaria intervention studies, atovaquone/proguanil has been used to treat any pre-existing malaria in the participants. In this setting, studies showed that the 3-day schedule provided protection against malaria for >4 weeks even in highly endemic areas [22,23]. Studies in volunteers in controlled environments in non-endemic countries have shown similar results [24,25]. Considering that the elimination half lives of atovaquone and proguanil are 2-3 days and 14-20 hours, respectively, the lengthy antimalarial activity cannot be explained by simple pharmacokinetics, and is likely to be attributed to the causal prophylactic effect of the drugs on parasites in the liver [5]. A summary of the evidence for atovaquone/proguanil's extended antimalarial activity, and therefore the rationale for its use in chemoprophylaxis, is provided in Table S1.

The 3-day schedule's extended antimalarial activity could potentially allow it to be used for prophylaxis, and the short duration of medications (3 days) might improve compliance in travellers. For trips of <4 weeks, travellers could complete the 3-day schedule prior to travel, and have a "drug-free holiday" [5]. For longer trips, the 3-day schedule could be repeated every 4 weeks to provide longer protection. For travellers spending more than three days in a malaria endemic area, the 3-day schedule is also cheaper than the standard daily schedule for atovaquone/proguanil. Other advantages include the ability to manage any side effects before departure (by changing to the standard schedule or different medication), avoiding the problem of not being able to swallow or absorb medications in case of gastrointestinal illness during travel, and avoiding the need to carry or buy medications overseas.

Atovaquone/proguanil is safe and well tolerated as prophylaxis in healthy travellers (1 tablet/day), and as treatment for malaria (4 tablets/day) [26-29]. However, tolerability of the 3-day schedule has not been assessed in the prophylaxis setting, when travellers are usually well, and milder side effects might be more be apparent. In this study, we investigated the compliance, tolerability and acceptability of the 3-day atovaquone/proguanil schedule for pre-travel malaria chemoprophylaxis.

Methods

Study design

A single-arm trial was conducted to assess the compliance, tolerability, and acceptability of a 3-day atovaquone/proguanil schedule. Four specialist travel medicine clinics from the Travel Medicine Alliance group in Australia participated: Dr Deb – The Travel Doctor,

Brisbane; Travel-Bug Vaccination Clinic, Adelaide; Health HQ, Gold Coast; and Travel Medicine Centre Perth.

Study population

Adults (≥18 years) travelling to malaria-endemic areas in Asia, Pacific Islands, and South/Central America for ≤4 weeks were eligible. Exclusion criteria included taking medications that interact with atovaquone/proguanil (metoclopramide, rifampicin, tetracyclines,fluvoxamine); pregnancy or planning pregnancy; significant medical conditions (i.e. diabetes, heart diseases, asthma, epilepsy, depression, renal or liver impairment, gastrointestinal disorders); and taking long-term antibiotics. Considering that our study was focused on assessing compliance, tolerability and acceptability (and not effectiveness), travellers to sub-Saharan Africa were excluded from the study because of the higher risk of malaria compared to other regions [1,30].

Travellers who required malaria prophylaxis were given the options of standard schedules of doxycycline, mefloquine, and atovaquone/proguanil, as well as the 3-day atovaquone/proguanil schedule. Choice of prophylaxis was based on multiple factors including time to departure, duration and side effects of the medications, daily versus weekly dosing, co-morbidities, and personal preference. Pros and cons of options were explained to potential participants, including the 'off-label' use of the 3-day schedule for prophylaxis. Cost was also discussed, and travellers or their employers paid for medications regardless of which option was chosen. All travellers who chose the 3-day schedule were enrolled in the study.

Sample size

Sample size was calculated to identify any differences in the prevalence of adverse reactions with the 3-day schedule in a prophylaxis setting, compared to reported adverse reactions for the standard prophylaxis dose, or the 3-day schedule when used for treatment [26]. Assuming a baseline prevalence of gastrointestinal side effects of up to 15% (i.e. diarrhoea, nausea, and abdominal pain) [26], 200 participants would be required to provide 90% power at a type I error of 0.05 to detect a 10% difference between groups. Assuming withdrawal or loss to follow-up of 10%, the study aimed for a target sample size of 220.

Informed Consent and Approvals

Information sheets were provided to all participants, and written informed consent was obtained before enrolment. The study was approved by the Australian National University Human Research Ethics Committee (2016/295), and registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12616000640404).

Study intervention and data collection

Participants were instructed to take 4 tablets of atovaquone/proguanil (250mg/100mg) per day (taken all at once) for 3 consecutive days, with the last dose taken at least one day before travel. Participants were encouraged to take each dose with a fatty meal (>24g) as there is evidence that dietary fat increases the absorption of atovaquone [31] and decreases the likelihood of gastrointestinal side effects.

Participants were asked to contact their clinic if they were unable to tolerate any of the doses, or if side effects were debilitating and they did not wish to continue. For these

participants, a doctor or nurse discussed alternative chemoprophylaxis regimens to ensure adequate protection against malaria.

Data were collected using three questionnaires, and a memory aid and symptom diary:

1. A travel medicine nurse completed an *enrolment questionnaire* with each participant. Information was collected on the current trip, previous history of malaria, travel to malaria endemic areas in the previous 12 months, previous experience with taking anti-malarial medications, past medical history, current medications and allergies.

2. A nurse telephoned the participants and completed a *pre-travel questionnaire* the day after the 3-day schedule was completed. The nurse confirmed whether the 3-day schedule was taken correctly and documented any side effects during and immediately after the schedule.

3. Within a week after return to Australia, a nurse telephoned the participants to complete a *post-trip questionnaire*, to collect information on any adverse reactions or diagnosis of malaria during or after travel. Participants were advised to contact the clinic if they were diagnosed with malaria after the post-travel questionnaire.

4. A *Memory Aid and Symptom Diary* was provided to record any symptoms and their intensity for 10 days after starting the 3-day schedule. Symptom severity was defined as mild, moderate, or severe based on the following criteria:

- Vomiting: 1-2 episodes in 24 hours; >2 episodes in 24 hours; required intravenous hydration
- Diarrhoea: 2-3 loose stools; 4-5 loose stools; 6 or more loose stools in 24 hours
- Mouth ulcers: Easily tolerated, able to eat and drink normally; discomfort, interfered with eating and drinking; incapacitating, great difficulty with eating and drinking

- Other symptoms: Easily tolerated, able to continue with normal activities; discomfort, interfered with normal daily activities; incapacitating, prevented normal activities.

Statistical analysis

All participants who started the 3-day schedule were included in the analysis. Descriptive statistics were used to report the characteristics of the participants. The outcomes (compliance, tolerability, acceptability) were estimated as the proportion of participants who completed the 3-days schedule and reported each outcome over the total number of participants who responded to the pre-travel questionnaire.

Multivariate logistic regression models were built to identify independent predictors of overall side effects, and specific side effects that were reported in >10% of participants. Predictor variables were defined *a priori* and included gender, age, comorbidities, allergies, taking atovaquone/proguanil with high-fat foods, and prior use of atovaquone/proguanil and/or other antimalarials. Predictor variables were entered using a stepwise forward selection in the regression models. All tests were two-tailed and *p*-value of <0.05 was deemed statistically significant. Analyses were conducted using Stata MP version 14 (StataCorp, College Station, TX, USA).

Results

Characteristics of the participants

A total of 233 participants were enrolled in the study from August 2016 to January 2018, of whom 215 (92.3%) completed the enrolment and pre-travel questionnaires, and were included

in the analysis. After return from their travels, 205 participants were successfully followed-up (Figure 1). No participants reported diagnosis of malaria while overseas or upon return.

Median age of participants was 43.8 (interquartile range [IQR] 28.9-57.8) years and 51.2% were female. Twenty-one participants (9.8%) reported a comorbidity, most commonly asthma (4.7%) and gastrointestinal diseases (3.3%). The majority of the participants reported previous travel to malaria-endemic countries (65.6%) and use of antimalarial medications (50.7%). Sixty-six participants (30.7%) reported previous use of atovaquone/proguanil and only three had previously experienced side effects to the medication (i.e. nausea in all three participants, diarrhoea and abdominal pain in one participant, and vomiting in another participant). Countries of destination included India, Cambodia, Vietnam, Papua New Guinea, Laos, Myanmar, Indonesia, Thailand, East Timor, Malaysia, Solomon Islands, Brazil, and Ecuador. The main reasons for choosing the 3-day schedule were that it was easier to remember (72.1%), required taking fewer tablets (54.0%), and to help scientific research (54.0%) (Table 1).

Compliance

The 3-day schedule was correctly completed by 210 of 215 participants (97.7%, 95% CI 94.7-99.2%). Two did not complete the schedule due to gastrointestinal side effects (diarrhoea, nausea, vomiting, or abdominal pain), two took the medication every second day or irregularly, while one discontinued because of an upper respiratory tract infection (Figure 1).

Tolerability

Among those that completed the 3-day schedule, side effects were reported in 91 participants (43.3%) (Figure 1); most commonly nausea (24.8%), diarrhoea (17.1%), tiredness (9.0%), headache (5.7%), and dizziness (5.7%). The prevalence of gastrointestinal side effects (33.8%) was higher than for the standard prophylaxis dose (15.9% [26], *p*-value <0.001), but similar to the 3-day schedule when used for treatment (40.5% [26], *p*-value = 0.13). Side effects were well tolerated, and interfered with their normal activities in only 3 (1.4%) participants. The majority of the side effects were mild (n=70, 33.3%), and only 10% of participants perceived the symptoms as moderate (n=16, 7.6%) or severe (n=5, 2.4%) (Figure 2 and S2). Side effects mainly occurred during the three days of the schedule (day 1 [25.7%], day 2 [27.6%], day 3 [19.5%]), and rapidly improved thereafter (day 4 [1.9%], day 5 [0.5%]). All side effects resolved before departure (S2 and S3). Among those who reported side effects, median duration of symptoms was 2 ([IQR] 1-2) days. Three-quarters reported that symptoms lasted for 1 day (n=44, 48.3%) or 2 days (n=25, 27.5%). Only 20 (22.0%) and 2 (2.2%) reported symptoms that lasted for 3 and 4 days, respectively. No participants reported duration of symptoms exceeding 4 days.

Multivariate logistic regression models revealed that females had higher odds of developing overall side effects (odds ratio [OR], 1.79; 95% confidence interval [CI], 1.02-3.14) and nausea (OR, 2.09; 95%CI 1.07-4.08). Younger participants had higher odds of reporting nausea and the odds decreased by 21% (OR 0.79, 95%CI 0.64-0.97) per decade increase in age. No independent predictors were identified for diarrhoea (Table 2).

Acceptability

After the trip, 196 participants (95.6%) responded that they would choose to take the 3-day schedule again for future trips. Among the 9 (4.4%) participants who would not use the 3-day schedule again, the main reason was that side effects were unacceptable (n=7) (Figure 1).

Discussion

Our study provides important data on the compliance, tolerability, and acceptability of the 3-day schedule of atovaquone/proguanil in healthy travellers, and the potential for using this schedule for malaria prophylaxis. The high compliance of (97.7%) is impressive compared to previous studies, which have reported 24-89% for the standard schedule of atovaquone/proguanil [29,32], 65-80% for proguanil [6,33], 60-79% for doxycycline [6,34], and 68-80% for mefloquine [6,33,34]. Considering that poor compliance to chemoprophylaxis is a major contributing factor to travel-related malaria, the 3-day schedule has the potential to significantly reduce malaria in travellers.

Although the 3-day schedule is known to be well tolerated when used to treat malaria, it is difficult to distinguish side effects (e.g. nausea, vomiting) from the symptoms of malaria. Our study showed that 4 tablets/day is well tolerated in healthy travellers and the prevalence of reported side effects were similar to those reported when used for treatment [16]. The majority of side effects were mild, limited to 1-2 days duration, and completely resolved before departure.

Our study also showed that the 3-day schedule was well accepted by travellers, with >95% indicating that they would choose this option again for future chemoprophylaxis. Travellers readily embraced the idea of ‘getting the malaria tablets out of the way before

departure', or 'not having to worry about malaria tablets if I am sick with diarrhoea and vomiting'. Further studies will be required to directly compare the compliance, acceptability and tolerability of the 3-day schedule against the standard atovaquone/proguanil prophylaxis schedule and its variations, including twice weekly dosage [35] or ceasing the medication one day after leaving a risk area [36].

The standard prophylaxis dosage of atovaquone/proguanil is expensive compared to other anti-malarial medications, and can be prohibitively so for long trips. For a four week stay in a risk area, the cost difference between standard daily atovaquone/proguanil (~$194 for 37 tablets) and the 3-day schedule (~$63 for 12 tablets) was ~AU$131 at the clinics where this study was conducted.

The results should be considered in light of the study's limitations. Compliance and acceptability were self-reported, and may be subject to participation bias. However, our participants actively sought pre-travel health advice from specialist travel clinics and are generally motivated to take malaria chemoprophylaxis, so it is unlikely for this group to falsely report compliance. Reports on side effects could have been influenced by recall bias, but this was minimised by use of a Memory Aid and Symptom Diary. We did not include a control group of travellers taking standard prophylaxis schedules of atovaquone/proguanil or other medications.

No participant was diagnosed with malaria during or after travel, although the study was not designed to, nor has the statistical power to assess the effectiveness of the 3-day schedule for prophylaxis. Studies on populations in malaria endemic areas have provided compelling evidence that the 3-day schedule provides antimalarial activity for up to 5-6 weeks [22-25].

However, further studies, including a larger sample size and higher risk destinations will be required to confirm effectiveness in non-immune travellers.

In an experimental malaria challenge study, heavily infected mosquitoes were allowed to feed on six non-immune volunteers who were given atovaquone/proguanil 1000mg/400mg 7 days earlier [37]. One developed parasitaemia 21 days post-challenge, but results were questionable because PCR and culture failed to confirm malaria. If the volunteer truly had parasitaemia, a single failure after such a severe challenge does not preclude the use of the 3-day schedule for prophylaxis, but signifies that like all other chemoprophylaxis, it is not 100% effective. The study also showed that chemoprophylaxis failure (in three volunteers, including two who used other schedules) was associated with poor absorption of atovaquone, and highlights the importance of taking the medications with a large (preferably fatty) meal [37].

Previous discussions on the long-lasting activity of atovaquone/proguanil raised concerns regarding development of drug resistance to atovaquone, because it has a longer half-life and will be present after proguanil has been eliminated [22,24,25]. Atovaquone resistance might also be more likely with prolonged or repeated use, e.g. repeating the 3-day schedule every 4 weeks in long-term travellers. However, a recent study provided reassuring evidence that atovaquone-resistant parasites are unable to be transmitted by mosquitoes [22]. Also, drug pressure on atovaquone/proguanil created by travellers is unlikely differ significantly between the standard and 3-day schedules.

In conclusion, our study showed that the 3-day schedule of atovaquone/proguanil is a promising option for malaria prophylaxis, with very high compliance rate, and was well tolerated and accepted by travellers. Further studies are required to assess effectiveness in non-immune travellers.

Acknowledgements

We will like to thank Prof Dennis Shanks (Australian Defence Force Malaria and Infectious Disease Institute, Brisbane, Australia) and Dr Andrew Ebringer (International SOS, Brisbane, Australia) for their contributions to study design and review of the manuscript. We would also like to thank all the participants, doctors, and nurses from the travel clinics that took part in the study.

Funding

CLL was supported by an Australian National Health and Medical Research Council Fellowship (grant number 1109035). The study was conducted as part of everyday clinical practice, and participants or their employers paid for the medications. No funding was received from any pharmaceutical companies.

Conflicts of interest

CLL and DJM are doctors, and LR and LM nurses, at privately owned, independent travel medicine clinics that provide advice and medications for malaria prophylaxis. The other authors do not have any conflicts of interest to declare.

References

1. Angelo KM, Libman M, Caumes E, et al. Malaria after International Travel: A Geosentinel Analysis, 2003-2016. Malar J, 2017;16:293.
2. Schlagenhauf P, Weld L, Goorhuis A, et al. Travel-Associated Infection Presenting in Europe (2008-12): An Analysis of Eurotravnet Longitudinal, Surveillance Data, and Evaluation of the Effect of the Pre-Travel Consultation. Lancet Infect Dis, 2015;15:55-64.
3. Wilson ME, Weld LH, Boggild A, et al. Fever in Returned Travelers: Results from the Geosentinel Surveillance Network. Clin Infect Dis, 2007;44:1560-1568.
4. Arguin P, Tan K (2017) Chapter 3 - Infectious Diseases Related to Travel. Centers for Disease Control and Prevention Yellow Book 2018: Health Information for International Travel. New York: Oxford University Press.
5. Shanks GD, Magill AJ, Freedman DO, Keystone JS, Bradley DJ, Steffen R. Drug-Free Holidays: Pre-Travel Versus During Travel Malaria Chemoprophylaxis. Am J Trop Med Hyg, 2007;77:1-2.
6. Laver SM, Wetzels J, Behrens RH. Knowledge of Malaria, Risk Perception, and Compliance with Prophylaxis and Personal and Environmental Preventive Measures in Travelers Exiting Zimbabwe from Harare and Victoria Falls International Airport. J Travel Med, 2001;8:298-303.
7. Piyaphanee W, Wattanagoon Y, Silachamroon U, Mansanguan C, Wichianprasat P, Walker E. Knowledge, Attitudes, and Practices among Foreign Backpackers toward Malaria Risk in Southeast Asia. J Travel Med, 2009;16:101-106.
8. Jute S, Toovey S. Knowledge, Attitudes and Practices of Expatriates Towards Malaria Chemoprophylaxis and Personal Protection Measures on a Mine in Mali. Travel Med Infect Dis, 2007;5:40-43.
9. Cunningham J, Horsley J, Patel D, Tunbridge A, Lalloo DG. Compliance with Long-Term Malaria Prophylaxis in British Expatriates. Travel Med Infect Dis, 2014;12:341-348.
10. Resseguier N, Machault V, Ollivier L, et al. Determinants of Compliance with Malaria Chemoprophylaxis among French Soldiers During Missions in Inter-Tropical Africa. Malar J, 2010;9:41.
11. Whitman TJ, Coyne PE, Magill AJ, et al. An Outbreak of Plasmodium Falciparum Malaria in U.S. Marines Deployed to Liberia. Am J Trop Med Hyg, 2010;83:258-265.
12. Creach MA, Velut G, de Laval F, et al. Factors Associated with Malaria Chemoprophylaxis Compliance among French Service Members Deployed in Central African Republic. Malar J, 2016;15:174.
13. Landman KZ, Tan KR, Arguin PM. Adherence to Malaria Prophylaxis among Peace Corps Volunteers in the Africa Region, 2013. Travel Med Infect Dis, 2015;13:61-68.
14. Pistone T, Guibert P, Gay F, et al. Malaria Risk Perception, Knowledge and Prophylaxis Practices among Travellers of African Ethnicity Living in Paris and Visiting Their Country of Origin in Sub-Saharan Africa. Trans R Soc Trop Med Hyg, 2007;101:990-995.
15. Robinson P, Jenney AW, Tachado M, et al. Imported Malaria Treated in Melbourne, Australia: Epidemiology and Clinical Features in 246 Patients. J Travel Med, 2001;8:76-81.
16. Luthi B, Schlagenhauf P. Risk Factors Associated with Malaria Deaths in Travellers: A Literature Review. Travel Med Infect Dis, 2015;13:48-60.
17. Newman RD, Parise ME, Barber AM, Steketee RW. Malaria-Related Deaths among U.S. Travelers, 1963-2001. Ann Intern Med, 2004;141:547-555.

18. Vliegenthart-Jongbloed K, de Mendonca Melo M, van Wolfswinkel ME, Koelewijn R, van Hellemond JJ, van Genderen PJ. Severity of Imported Malaria: Protective Effect of Taking Malaria Chemoprophylaxis. Malar J, 2013;12:265.
19. Stoney RJ, Chen LH, Jentes ES, et al. Malaria Prevention Strategies: Adherence among Boston Area Travelers Visiting Malaria-Endemic Countries. Am J Trop Med Hyg, 2016;94:136-142.
20. Bocci G, Troiano G, Golinelli D, Verzuri A, Rossi S, Nante N. Compliance with Malaria Chemoprophylaxis in Travelers: A Systematic Review. Eur J Public Health, 2016;26:ckw174.229.
21. Goodyer L, Rice L, Martin A. Choice of and Adherence to Prophylactic Antimalarials. J Travel Med, 2011;18:245-249.
22. Polhemus ME, Remich S, Ogutu B, et al. Malaria Treatment with Atovaquone-Proguanil in Malaria-Immune Adults: Implications for Malaria Intervention Trials and for Pre-Exposure Prophylaxis of Malaria. Antimicrob Agents Chemother, 2008;52:1493-1495.
23. Shanks GD, Ragama BO, Oloo AJ. Time to Reappearance of Malaria Parasites Following Various Drug Treatment Regimens in a Holoendemic Area of Western Kenya. Trans R Soc Trop Med Hyg, 1999;93:304-305.
24. Butcher GA, Sinden RE. Persistence of Atovaquone in Human Sera Following Treatment: Inhibition of Plasmodium Falciparum Development in Vivo and in Vitro. Am J Trop Med Hyg, 2003;68:111-114.
25. Edstein MD, Kotecka BM, Anderson KL, et al. Lengthy Antimalarial Activity of Atovaquone in Human Plasma Following Atovaquone-Proguanil Administration. Antimicrob Agents Chemother, 2005;49:4421-4422.
26. GlaxoSmithKline Australia Pty Ltd. Product Information - Malarone® Tablets (250/100). 2016. Available: http://au.gsk.com/media/339251/malarone_and_malarone_junior_pi_008_approved.pdf
27. Nakato H, Vivancos R, Hunter PR. A Systematic Review and Meta-Analysis of the Effectiveness and Safety of Atovaquone Proguanil (Malarone) for Chemoprophylaxis against Malaria. J Antimicrob Chemother, 2007;60:929-936.
28. Overbosch D, Schilthuis H, Bienzle U, et al. Atovaquone-Proguanil Versus Mefloquine for Malaria Prophylaxis in Nonimmune Travelers: Results from a Randomized, Double-Blind Study. Clin Infect Dis, 2001;33:1015-1021.
29. Petersen E. The Safety of Atovaquone/Proguanil in Long-Term Malaria Prophylaxis of Nonimmune Adults. J Travel Med, 2003;10 Suppl 1:S13-15; discussion S21.
30. World Health Organization. World Malaria Report 2017. 2017. Available: http://www.who.int/malaria/publications/world_malaria_report/en/
31. Rolan PE, Mercer AJ, Weatherley BC, et al. Examination of Some Factors Responsible for a Food-Induced Increase in Absorption of Atovaquone. Br J Clin Pharmacol, 1994;37:13-20.
32. DePetrillo JC, Singer C, Bergagnini IA, Kolakowski P, Edwards B, Smith MA. Assessment of Adherence to Atovaquone-Proguanil Prophylaxis in Travelers. J Travel Med, 2010;17:217-220.
33. Hoebe C, de Munter J, Thijs C. Adverse Effects and Compliance with Mefloquine or Proguanil Antimalarial Chemoprophylaxis. Eur J Clin Pharmacol, 1997;52:269-275.
34. Saunders DL, Garges E, Manning JE, et al. Safety, Tolerability, and Compliance with Long-Term Antimalarial Chemoprophylaxis in American Soldiers in Afghanistan. Am J Trop Med Hyg, 2015;93:584-590.
35. Lachish T, Bar-Meir M, Eisenberg N, Schwartz E. Effectiveness of Twice a Week Prophylaxis with Atovaquone-Proguanil (Malarone(R)) in Long-Term Travellers to West Africa. J Travel Med, 2016;23.

36. Leshem E, Meltzer E, Stienlauf S, Kopel E, Schwartz E. Effectiveness of Short Prophylactic Course of Atovaquone-Proguanil in Travelers to Sub-Saharan Africa. J Travel Med, 2014;21:82-85.
37. Deye GA, Miller RS, Miller L, et al. Prolonged Protection Provided by a Single Dose of Atovaquone-Proguanil for the Chemoprophylaxis of Plasmodium Falciparum Malaria in a Human Challenge Model. Clin Infect Dis, 2012;54:232-239.

Table 1. Participants' characteristics

Demographics	
Female (%)	110 (51.2)
Median age (IQR) [range]	43.8 (28.9-57.8) [18.3-80.7]
Medical history	
Comorbidities (%)	21 (9.8)
Asthma (%)	10 (4.7)
Gastrointestinal diseases (%)	7 (3.3)
Cardiovascular diseases (%)	3 (1.4)
Depression (%)	3 (1.4)
Allergies to medications (%)	22 (10.2)*
Prior exposure to malaria	
Travelled to malaria endemic country (%)	141 (65.6)
Prior malaria infection (%)	6 (2.8)
Prior use of antimalarial medication (%)	109 (50.7)
Atovaquone/proguanil (%)	66 (30.7)†
Doxycycline (%)	50 (23.3)
Proguanil (%)	21 (9.8)
Mefloquine (%)	16 (7.4)
Chloroquine (%)	16 (7.4)
Travel destination	
India (%)	78 (36.3)
Cambodia (%)	34 (15.8)
Vietnam (%)	23 (10.7)
Laos (%)	19 (8.8)
Papua New Guinea (%)	17 (7.9)
Thailand (%)	17 (7.9)
Myanmar (%)	16 (7.4)
Malaysia (%)	12 (5.6)
Indonesia (%)	11 (5.1)
East Timor (%)	10 (4.7)
Solomon Islands (%)	4 (1.9)
Brazil (%)	3 (1.4)
Ecuador (%)	3 (1.4)
Reason for choosing 3-day schedule	
Easier to remember (%)	155 (72.1)
Requires fewer tablets (%)	116 (54.0)
Help scientific research (%)	116 (54.0)
Lower cost (%)	68 (31.6)

* Most common allergies were to penicillins and NSAIDs. † Only 3 participants reported prior side effects. *IQR* interquartile range

Table 2. Univariate and multivariate logistic regression for predictors of side effects

	Overall side effects		Nausea		Diarrhoea	
	Univariate model OR (95%CI)	Multivariate model OR (95%CI)	Univariate model OR (95%CI)	Multivariate model OR (95%CI)	Univariate model OR (95%CI)	Multivariate model OR (95%CI)
Gender –Female	**1.88 (1.08-3.27)**	**1.79 (1.02-3.14)**	**2.26 (1.18-4.33)**	**2.09 (1.07-4.08)**	1.28 (0.62-2.63)	-
Age (per decade increase)	0.88 (0.74-1.05)	0.91 (0.76-1.08)	**0.78 (0.63-0.95)**	**0.79 (0.64-0.97)**	0.98 (0.78-1.22)	-
Presence of comorbidities	1.34 (0.53-3.39)	-	0.74 (0.24-2.32)	-	1.23 (0.39-3.94)	1.64 (0.56-4.84)
Allergies to medications	1.50 (0.61-3.70)	-	1.24 (0.46-3.40)	-	1.59 (0.54-4.67)	-
Taking atovaquone/proguanil with high-fat foods	1.37 (0.77-2.45)	-	1.68 (0.88-3.21)	-	0.86 (0.39-1.86)	-
Prior use of antimalarial medication	0.90 (0.52-1.55)	-	1.17 (0.62-2.19)	-	0.73 (0.35-1.50)	-
Prior use of atovaquone/proguanil	0.95 (0.53-1.71)	-	1.21 (0.62-2.36)	1.46 (0.73-2.91)	0.68 (0.30-1.55)	0.67 (0.30-1.53)

OR odds ratio; *CI* confidence interval. Boldface data indicate statistically significant results

Figure legends

Figure 1. Participants enrolment and follow-up flowchart

Figure 2. Percentage of participants who reported side effects, stratified by intensity

Figure 1

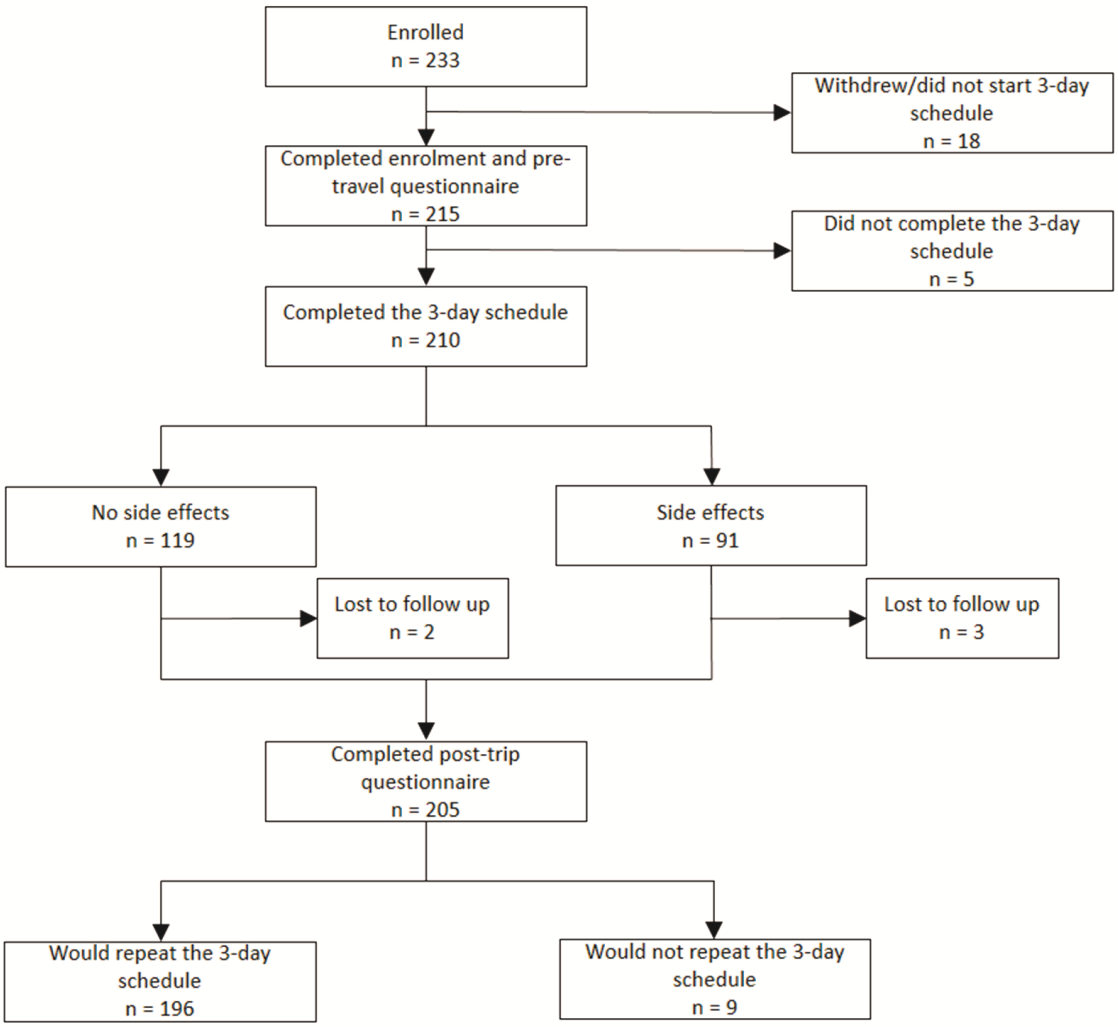

Figure 2